Kidney International, Vol. 18 (1980), pp. 103–109

Treatment of end-stage renal disease in children: A 15-year experience

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Treatment of end-stage renal disease in children: A 15-year experience. From 1964 to 1979, 154 children 1 to 16 years of age with end-stage renal disease (ESRD) were treated in a regional pediatric dialysis and transplant program. The incidence of ESRD was 1.6 per million total population per year. The survival rate of children undergoing dialysis for an average of 10 months was 93%. After living donor kidney transplantation (LD), patient survival rates in 60 children were 89% at 5 years, 83% at 10 years, and 74% at 15 years. After cadaver donor kidney transplantation (CD), patient survival rates in 85 children were 70% at 5 and 10 years. LD kidney survival was 71% at 5 years, 55% at 10 years, and 40% at 15 years, whereas CD kidney survival was 43% at 5 years and 31% at 10 years. The survival of first and second transplants was similar. Patient and kidney survival have improved since 1972. The survival rate of 26 children 1 to 5 years of age was 46%, but patients with Wilms' tumor accounted for most of the deaths. We attribute these favorable long-term results in children to an integrated program of dialysis and transplantation with special pediatric facilities.

Traitement de l'insuffisance rénale terminale chez l'enfant: 15 Ans d'expérience. De 1964 à 1979, 154 enfants de 1 à 16 ans atteints d'insuffisance rénale terminale (ESRD) ont été traités dans le cadre d'un programme pédiatrique régional de dialyse et transplantation. L'incidence de l'ESRD a été de 1,6 par million de population totale et par an. Le taux de survie d'enfants en dialyse pendant une durée moyenne de 10 mois était de 93%. Après transplantations avec des reins de donneurs vivants (LD), le taux de survie chez 60 enfants était de 89% à 5 ans, 83% à 10 ans, et 74% à 15 ans. Après transplantations de reins de cadavres (CD), le taux de survie chez 85 enfants était de 70% à 5 et à 10 ans. La survie des reins de donneurs vivants était de 71% à 5 ans, 55% à 10 ans, et 40% à 15 ans, alors que la survie des reins de cadavres était de 43% à 5 ans et 31% à 10 ans. La survie des premiers et deuxièmes transplants a été semblable. La survie des malades et des reins a été améliorée depuis 1972. Le taux de survie de 26 enfants âgés de 1 à 5 ans a été de 46% et la plupart des décès sont ceux des malades atteints de tumeur de Wilm. Nous attribuons ces résultats à long terme favorables chez des enfants à un programme de dialyse et de transplantation intégré assorti de modalités pédiatriques particulières.

The first successful kidney transplant between nonidentical individuals was performed in 1959, and the first program of chronic hemodialysis was started the following year. In the two decades that have ensued, the lives of thousands of patients with end-stage renal disease (ESRD) have been prolonged by the complementary use of these two forms of treatment. The incidence and causes of ESRD and the results of treatment in adults have been described extensively, and there are reviews of more limited experience in children [1–5]. At the University of California, San Francisco, two renal transplants were performed in children in 1964, and a comprehensive, regional program for the care of children with ESRD was initiated in 1966 [6–7]. In cooperation with other physicians in the area, this program has coordinated the care of all children with ESRD in the well-defined geographic area of Northern California-Northern Nevada. Dialysis and transplantation have been performed in one center with the same physicians and staff involved in both forms of therapy. In the course of this experience, the incidence of ESRD in children, the interrelationship of dialysis and transplantation in the treatment regimen, and the outcome of treatment over periods as long as 15 years have been defined.

Methods

This report considers children who were 1 to 16 years of age when they reached end-stage renal disease. Children who died with acute, potentially reversible, renal disease were not included. The incidence of ESRD in this age group was determined for the area of Northern California-Northern Nevada from referrals to our center, which is the only pediatric ESRD center in the area, and from a survey of adult dialysis units. Incidence is expressed as

Received for publication August 31, 1979
and in revised form December 17, 1979

0085-2538/80/0018-0103 $01.40

cases per million total population per year. The mean population of the area during the study was 8.3 million.

One hundred fifty-four children were treated with dialysis or transplantation, or both, in our center. Eighty-three received dialysis in the pediatric outpatient dialysis unit. One hundred forty-five received renal transplants, 74 after dialysis in the pediatric unit and 71 after short periods of inpatient dialysis, dialysis in adult units, or without previous dialysis. Followup of the 154 children was complete in May, 1979, and is outlined in the section *Outcomes of Treatment*. All deaths were included in survival calculations even if the children had transferred to other dialysis or transplant programs. Deaths of 2 children who returned to dialysis after transplantation were calculated as transplant deaths; one of these deaths occurred in the pediatric dialysis program and was also calculated as a dialysis death.

Patient and kidney survival rates after transplantation were calculated by actuarial methods [8] and expressed as cumulative survival curves. Although survival rates were calculated for all years during which at least 1 patient or kidney was at risk, rates calculated from samples of less than 10 were not considered to have clinical significance. Differences between survival curves were determined by the Breslow modification of the Wilcoxon test [9].

Basic immunosuppression after transplantation was azathioprine, 2 to 3 mg/kg, and prednisone, 2 to 4 mg/kg, with progressive reduction of the steroid dose. Irradiation of the kidney, actinomycin D, antilymphocyte globulin, and pulse doses of methylprednisolone were also used during various periods in the program. The use of methyl prednisolone was discontinued, and the amount of immunosuppression used to treat rejections was decreased in September, 1972 [10]. Beginning in 1970, children with good renal function 6 months after transplantation were treated with alternate-day prednisone [11].

Selection of living donor kidneys was based on the results of HL-A typing and, after 1971, also on the results of mixed lymphocyte culture (MLC) reactions [12]. Of the 60 donors of primary kidneys, there were 50 parents, 7 siblings, of whom 4 were HL-A identical, 2 grandparents, and 1 uncle. Recipients of cadaver kidneys were selected on the basis of HL-A typing, but all cadaver kidneys were used regardless of the match. No 4-antigen-match cadaver transplants were performed.

Results

Incidence. The number of children 1 to 16 years of age with ESRD from Northern California-Northern Nevada identified by year is shown in Table 1. After 1967, the number was fairly constant until the years 1975–1978 when more marked fluctuations occurred. The mean incidence of ESRD for the years 1968–1978 was 1.58 per million. The mean incidence in three age groups, 1 to 5, 6 to 10, and 11 to 15 years was 0.31, 0.42, and 0.87 per million, respectively.

Treatment. After 1967, when the chronic dialysis and cadaver transplant programs were established, all children with ESRD were considered for treatment, and no a priori selection criteria were used. Children with malignancies, systemic diseases, and mental retardation were treated. Only 3 children were excluded; each was less than 6 years of age and had severe physical and developmental retardation.

The age distribution of the 154 children who were treated is shown in Fig. 1. The mean age was 10 years. The causes of renal failure are listed in Table 2. Children with systemic or "high-risk diseases" who were treated included 9 with Wilms' tumor, 3 with cystinosis, and 2 with lupus erthematosus.

Dialysis. The mean duration of dialysis of the 83 children was 10 months (range, 1 to 60 months). Six were treated with hemodialysis in the home, 4 with peritoneal dialysis in the home, and the remainder with hemodialysis in the center. Seventy four received transplants and 14 of these returned to dialysis after rejection. Four infants, 15 to 23 months of age, were dialyzed for periods of 3 to 15 months. There were six deaths; three caused by complications of Wilms' tumor and one each by vasculitis, pneumonia, and liver failure. Four of the children who died were less than 6 years of age. The survival rate was 93%.

Transplantation. The survival rate of 60 children who received first transplants from living donors was 85%, and the survival rate of 85 children who received first transplants from cadaver donors was 76%. The survival rate of all children treated with dialysis, transplantation, or both, was 78%.

Patient-survival curves after transplantation are shown in Fig. 2. After living-donor transplantation, six of nine deaths occurred during the first 3 years, and 1 patient died during the 12th year. The 2 children who received transplants in 1964 were alive at 15 years, and the cumulative survival rate was 74%. After cadaver-donor transplantation, all of the deaths occurred during the first 5 years, and the cu-

mulative survival rate thereafter was 70%. The difference between the curves was significant, $P < 0.05$.

The primary cause of death after transplantation was infection (Table 3). Two children who rejected kidneys died from uremia after the decision was made not to undergo further treatment, and 2 children undergoing dialysis after rejection died. There was one death from Wilms' tumor, and 4 other children with Wilms' tumor died of infection. Ten of the deaths occurred in the group of 20 children who were less than 6 years of age at transplantation. Survival rates calculated for three age groups, 1 to 5 years, 6 to 10 years, and 11 to 16 years, were 50%, 76%, and 88%, respectively.

Kidney survival curves are shown in Fig. 3 for 60 primary living-donor kidneys, 85 primary cadaver kidneys, and 27 second kidneys, all but 3 of which were cadaver kidneys. The survival rates of primary living donor kidneys were 86% at 1 year, 81% at 2 years, and 55% at 10 years, whereas the survival rates of primary cadaver kidneys were 65% at 1 year, 55% at 2 years, and 31% at 10 years. The difference between the curves was significant, $P < 0.02$. The results of second transplants were similar to the results of primary cadaver transplants. Five third transplants were performed, and three were functioning at followup. The cause of kidney loss in surviving patients was immunologic rejection in all but 3 patients; 2 children had recurrence of glomerulonephritis, and 1 required nephrectomy following spontaneous renal decapsulation.

Table 1. Number of children with end-stage renal disease in Northern California—Northern Nevada

1966	6	1971	11	1976	20
1967	5	1972	15	1977	9
1968	11	1973	12	1978	23
1969	13	1974	16		
1970	12	1975	6		

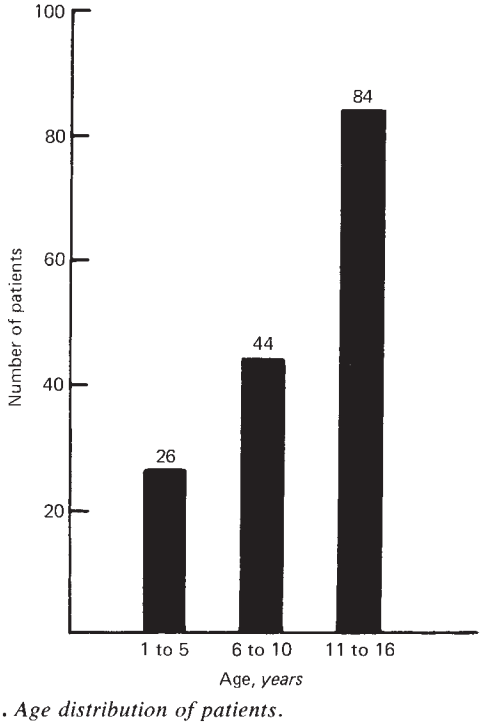

Fig. 1. *Age distribution of patients.*

Table 2. Cause of renal failure

Disease	No. of cases by age group		
	1 to 5 yr	6 to 10 yr	11 to 16 yr
Chronic glomerulonephritis	7	15	33
Obstructive uropathy	1	2	17
Dysplasia-hypoplasia	2	9	5
Pylonephritis	1	4	6
Wilms' tumor	9[a]	—	—
Medullary cystic disease	—	1	8
Hemolytic-uremic syndrome	2	6	1
Congenital nephrosis	3	—	—
Cystinosis	—	3	—
Lupus nephritis	—	—	2
Anaphylactoid purpura nephritis	—	1	1
Infantile polycystic kidneys	—	1	1
Interstitial nephritis	1	—	—
Hereditary syndromes			
Renal-retinal dysplasia	—	—	4
Alport's	—	1	3
Nail patella	—	—	1
Lawrence-Moon-Biedl	—	—	1
Charcot-Marie-Tooth	—	—	1
Jeune's	—	1	—
Total	*26*	*44*	*84*

[a] Seven bilateral, two unilateral with cortical necrosis of the other kidney

The amount of immunosuppression used to treat rejections was reduced in 1972. Following this change, the 2-year patient survival improved from 89% to 100% for recipients of living donor kidneys and 61% to 94% for recipients of cadaver kidneys. Two-year cadaver-kidney survival also improved, from 46% to 58%, but living-donor kidney survival was unchanged.

Kidney survival was plotted on semilog paper for all living donor kidneys and for all cadaver kidneys for the years during which at least 10 kidneys were at risk (Fig. 4). The fractional loss rates of both living-donor kidneys and of cadaver kidneys were quite constant after the second year, and survival rates for these periods were indicated by lines of regression. Survival half-life times calculated for these periods of constant risk were 13.5 years for

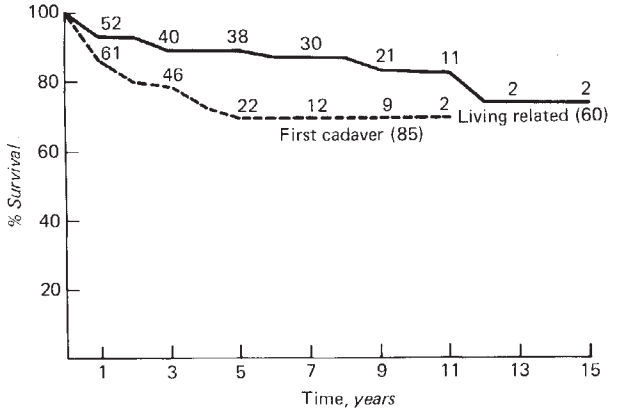

Fig. 2. *Patient survival after transplantation.* Numbers above the line refer to patients at risk. Numbers in parentheses denote total number of patients.

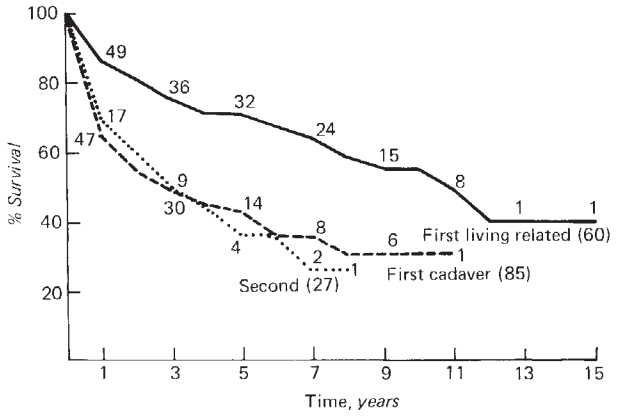

Fig. 3. *Kidney survival after transplantation.* Numbers are defined in Fig. 2.

living-donor kidneys and 6.8 years for cadaver kidneys.

The most recent serum creatinine concentration of each patient with a functioning kidney was plotted as a function of time after transplantation (Fig. 5). Of 38 children with kidneys functioning more than 5 years, 28 had serum creatinine concentrations ≤ 1.5 mg/dl.

Outcomes of treatment. The status of each of the 154 children at followup was examined in relation to the most recent treatment event—either the initiation of dialysis or the most recent transplant (Fig. 6). Thirty-four children (22%) were dead, 26 (17%) were undergoing dialysis, and 92 (60%) had functioning kidneys.

Discussion

During the 15 years this program has been in operation, dialysis and transplantation have evolved from experimental treatments for a handful of chil-

Table 3. Cause of death, transplant

Infection	
Bacterial	9
Pneumocystis	2
Varicella	2
Viral?	2
Fungal	1
Uremia (rejection)	2
Dialysis	2
Cerebral hemorrhage	2
Transplant lung	1
Operative	1
GI bleeding	1
Liver failure	1
Wilms' tumor	1
Automobile accident	1
Unknown	1
Total	*29*

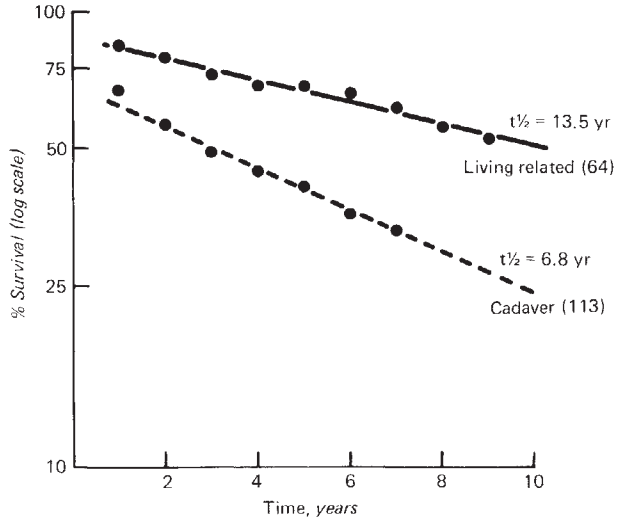

Fig. 4. *Kidney survival after transplantation, including secondary transplants (semi-log scale).*

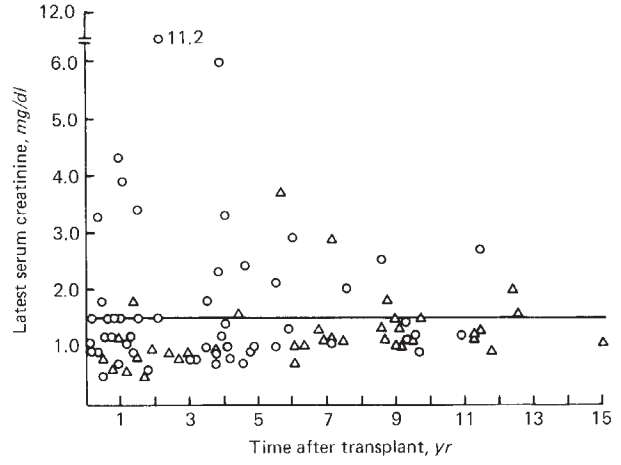

Fig. 5. *Most recent serum creatinine concentration of each patient with a functioning kidney.* Δ = living donor kidneys, ○ = cadaver kidneys.

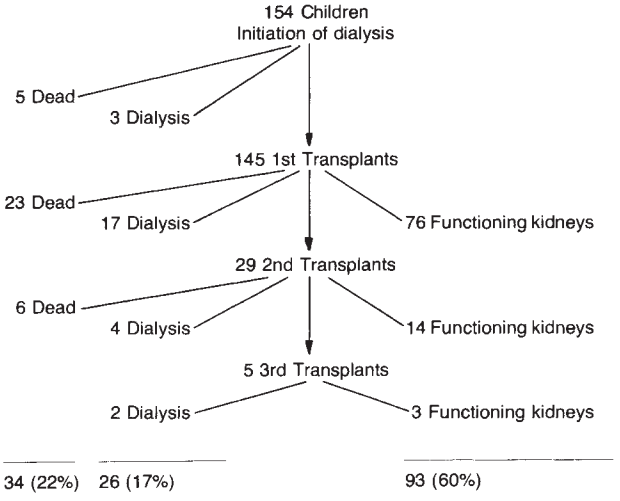

Fig. 6. *Outcomes of treatment including results of second transplants in other institutions.* One patient discontinued dialysis after 15 months.

dren to accepted therapy for thousands. A number of observations and conclusions pertinent to this evolution can be drawn from our experience.

There are few reliable data on the incidence of ESRD in children. Although incidence figures as high as 3.5 per million have been derived from death certificate data, alone [13] or in combination with a physician-hospital survey [14], figures derived from surveys of nephrology units have been lower—0.75 to 1.5 per million [15]. In the only other study assessing sequential data from a population [16], the incidence in children 0.5 to 16 years was 1.36 per million.

In our program, there were yearly variations in the number of children presenting with ESRD, but the average for consecutive 2-year periods was fairly constant over an 11-year period. It is likely that some children with ESRD and severe congenital anomalies, severe mental retardation, or systemic illness were not referred, but these children are rarely candidates for dialysis and transplantation, and the incidence of ESRD of 1.6 per million is probably a reasonable estimate in planning treatment facilities for children. We did not encourage referrals of infants less than a year of age, and the incidence of ESRD and indications for treatment in this age group remain to be defined.

The incidence of children entering treatment was 1.3 per million in the 1 to 14 age group. This is higher than the incidence in any European country except the Netherlands [5], and reflects the fact that patterns of referral to our center are well established and may also reflect our policy of considering all children for treatment regardless of size and underlying disease.

The results of treatment were evaluated in terms of patient survival and the success of the program in maintaining children with functioning kidneys. Because most children received transplants after short periods of dialysis, we could not compare long-term survival with the two forms of treatment, but the 1-year survival with dialysis, 90%, was comparable to the 1-year survival after living-donor transplantation, 93%, and cadaver donor transplantation, 86%. Children undergoing dialysis invariably had complications of uremia and the treatment regimen, however, whereas transplantation offered the potential for return to a normal life, and children and families all regarded a well-functioning transplant as the ultimate goal of treatment.

The results were influenced by patient age and renal disease. A large number of young children, 1 to 5 years, were treated, and survival rates in these children were lower than they were in older children, a finding in agreement with reports from dialysis [17] and transplant [18] registries but contrary to the experience of another large transplant program [19]. Of the 26 children in this age group, 9 had Wilms' tumor as their underlying disease, however, and they accounted for more than one half of the deaths. When these children are excluded from calculations, the survival rate in the 1 to 5 age group after transplantation is 64%, and the survival rate of all children after transplantation is 83%.

Despite treatment of high-risk patients, long-term patient survival was good. Of 30 children who started treatment more than 10 years ago, 20 (67%) were alive at followup, 15 with functioning kidneys. Eighty percent of children who received transplants over a 15-year period were alive compared with 74% over a 10-year period in Minneapolis [1], 86% over a $9^1/_2$-year period in Los Angeles [3], and 78% over a $12^3/_4$-year period in Cincinnati [4]. In transplant programs where most of the patients were adults, survival was 61% over a 25-year period in Boston [20] and 65% over a $13^3/_4$-year period in Denver [21].

Kidney survival, 71% for living-donor kidneys and 43% for cadaver kidneys at 5 years, was better than that reported from the Transplant Registry [22] and similar to that achieved at two of the pediatric centers cited above [1, 3]. To predict survival beyond the 15 years covered in this report, we used the method of Opelz, Mickey, and Terasaki [23], who showed that the fractional loss rates of both living-donor kidneys and cadaver kidneys were

constant after the second year and could be described by half-life survival times. Projected kidney survival for our patients was approximately 30% for living donor kidneys and 10% for cadaver kidneys at 20 years. This prediction of prolonged survival is supported by the observation that most of the children with kidneys functioning longer than 5 years have serum creatinine concentrations $\leq$ 1.5 mg/dl. In our experience, late graft loss has invariably been preceded by chronic rejection and elevated serum creatinine concentrations beginning in the first few years after transplantation.

Although the results expressed by survival curves and projected survival times are favorable, they are based on all transplants performed since 1964 and do not accurately reflect the chances for success of transplants performed at the present time. Patient survival and cadaver kidney survival have improved markedly in recent years. Although this improvement has been attributed to changes in immunosuppressive therapy instituted in 1972 [10], other changes, such as the introduction of the MLC test, and the fact that the last transplant for Wilms' tumor was performed in 1971, may have also played a role. It is also likely that some of the difference in results before and after 1972 reflects gradual improvement from accumulated experience rather than specific changes in the transplant regimen.

Our experience emphasizes the benefits derived when living-donor rather than cadaver kidneys are used for transplantation. Not only were patient and kidney survival better for recipients of living-donor kidneys, but fewer children with functioning living-donor kidneys, 18%, had serum creatinine concentrations > 1.5 mg/dl at followup than did children with functioning cadaver kidneys, 29%. Because good renal function is the criterion for initiating alternate-day prednisone therapy in our program, children with living-donor kidneys were more likely to receive the benefits of this regimen, including normal growth [11], than were children with cadaver kidneys.

We attribute the favorable results in children to an integrated program of dialysis and transplantation with special facilities for children. Because the numbers of children with ESRD are small, we, as well as others, have been able to treat all children in a region in a single facility. The same physicians and other health care personnel have been involved in both forms of therapy. Transitions between dialysis and transplantation have been facilitated, and children with multiple rejection episodes after transplantation have electively returned to dialysis rather than undergoing prolonged high-dose immunosuppressive therapy. The complementary use of the two treatments has contributed to low mortality and a high rate of retransplantation, and 64% of recipients over a 15-year period have survived with functioning grafts. These results, and those from other pediatric programs, demonstrate that dialysis and transplantation are effective treatments which can extend life and provide long-term benefits for children with ESRD.

Acknowledgments

This work was supported in part by the State of California, Department of Health Services, Chronic Disease Control Section, Contract #78-62130. We acknowledge the contributions of Drs. J. Najarian, S. Kountz, and K. Cochrum to the pediatric transplant program and the assistance of R. Duca in evaluating results.

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